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DOCKET NO.: CP 380G
Application No.: 10/789,604
Office Action Dated: December 1, 2006

PATENT
REPLY FILED UNDER EXPEDITED PROCEDURE PURSUANT TO 37 CFR § 1.116

REMARKS

Claims 1, 3 to 12, and 16 to 18 are pending in the application. No claims have been amended, canceled, or added, herein. Applicants respectfully request reconsideration of the rejections of record in view of the following remarks.

Alleged Obviousness

The rejection of claims 1 to 13 and 16 to 18 under 35 U.S.C. § 103(a) as allegedly obvious over Chinese Patent number CN 1079391 ("the 391 patent") in view of U.S. Patent No. 6,720,011 ("the Zhang patent"), Shimotsuura, S., *Journal of Tokyo Dental College Society*, 1986, 86(8) 1237-1253 ("the Shimotsuura article"), and U.S. Patent No. 5,748,699 ("the Smith patent") has been maintained. Applicants again respectfully request reconsideration and withdrawal of the rejection because the Office has failed to establish *prima facie* obviousness.

To establish *prima facie* obviousness, the Patent Office must provide objective evidence that the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, contains some suggestion or incentive that would have motivated those of ordinary skill in the art to modify a reference or to combine references. *In re Lee*, 61 U.S.P.Q.2d 1430, 1433 (Fed. Cir. 2002); *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1998). And the proposed modification or combination of the prior art ***must have had a reasonable expectation of success***, determined from the vantage point of those of ordinary skill in the art, at the time the invention was made. *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991).

"[W]hether a particular combination might be 'obvious to try' is not a legitimate test of patentability." *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988). "Obvious to try" situations arise where it might have been obvious to "explore a new technology or general approach that seemed to be a promising filed of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). *See also Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.ed. 1367, 1380 (Fed. Cir. 1986)(stating that "At *most*, these articles

are invitations to try monoclonal antibodies in immunoassays but do not suggest how that end might be accomplished.")(emphasis in original).

Applicants respectfully submit that the Office has failed to establish *prima facie* obviousness because it has failed to demonstrate that the teachings and suggestions that can allegedly be gleaned from the proposed combination of the cited references would have had a reasonable expectation of success, determined from the vantage point of those of ordinary skill in the art, at the time the invention was made. Assuming, for the sake of argument, that those skilled in the art would have been motivated to combine the teachings of the cited references, which applicants do not concede, at most the combination *may* have rendered the claimed methods obvious to try, but it *would not* have rendered the methods *prima facie* obvious because those skilled in the art ***would not have reasonably expected*** that a combination of arsenic trioxide and radiation could have been successfully used to treat colon, ovarian, renal, bladder, or prostate cancer in humans at the time of the invention.

As discussed in the response to the official action dated June 23, 2006, the 391 patent indicates that arsenic preparations had been reported in the literature as having been used for the treatment of skin and cervical cancers.[1] The invention described in the patent relates to improved arsenic preparations, which the patentees speculate could be used for the treatment of body surface and body cavity tumors.[2] Notably, *the patent contains absolutely no experimental evidence indicating that the described arsenic preparations are efficacious* against body surface and body cavity tumors, much less against colon, ovarian, renal, bladder, or prostate cancer. The 391 patent thus states that arsenic preparations had been demonstrated to be effective against skin and cervical cancers, but provides no other evidence of efficacy against any other tumor type. Although the Office asserts that "CN 1079391 teaches efficacy of arsenic against body cavity tumors,"[3] the 391 patent provides absolutely no evidence that arsenic preparations are effective against body cavity tumors generally. Rather, the patent cites literature reporting that arsenic preparations had been successfully used to treat *skin and cervical cancers only*.

[1] English translation, pages 6 to 7.
[2] English translation, page 7, first full paragraph.
[3] Office action dated December 1, 2006, page 3.

Similar to the 391 patent, the Zhang patent provides evidence that an arsenic preparation is efficacious against only a single tumor type, while asserting that the preparation is effective against other tumor types. The Zhang patent states that the invention is directed to a composition that contains arsenic trioxide, and asserts that the composition can be used to treat leukemia, hepatoma, and lymphoma.[4] Notably, however, the patent only provides experimental evidence demonstrating that the composition is effective against leukemia.[5] The Office asserts, however, that "Zhang broadly teaches efficacy of arsenic trioxide against cancers, including liver cancer, and a strong abruptive effect on the membranes of cancer cells and inhibition of DNA/RNA synthesis."[6] As just discussed, the Zhang patent *asserts* that the described arsenic composition can be used to treat leukemia, hepatoma, and lymphoma, *but provides absolutely no evidence of efficacy* of the composition against hepatoma and lymphoma. Moreover, the patent states that the described arsenic compositions inhibit DNA/RNA synthesis in *leukemia cells only*, not in cancer cells generally.[7] Finally, one portion of the patent states that the "composition of the present invention exert [*sic*] a strong abruptive effect on the membranes of cancer cells, such as leukemic cells,"[8] while another portion of the patent states that this effect is limited only to leukemic cells: "[l]aboratory experiments indicate that the composition shows a strong abruptive effect on the membranes of leukemic cells."[9]

Those skilled in the art, necessarily trained in the rigors of the scientific method, would simply not accept as true assertions regarding the efficacy of a particular substance for the treatment of specific conditions if the assertions were unsupported. Rather, those skilled in the art would only accept that a particular substance could be successfully used to treat specific conditions if experiments had been performed that produced data demonstrating the efficacy of the substance against the conditions. Accordingly, in contrast to the Office's assertions, due to the absence of any supporting data whatsoever, those skilled in the art would not reasonably accept the assertions made in the 391 and Zhang patents regarding the

[4] Col. 1, lines 33 to 35.
[5] Col. 2, line 60 to col. 3, line 27.
[6] Office action dated December 1, 2006, page 4.
[7] Col. 1, lines 61 to 62 and col. 2, lines 23 to 27.
[8] Col. 1, lines 58 to 61.
[9] Col. 2, lines 23 to 27.

efficacy of arsenic preparations against body cavity tumors generally, hepatoma, and lymphoma.

The Shimotsuura article does not compensate for the deficiencies of the 391 and Zhang patents. As discussed in the reply filed September 15, 2006, the article describes the efficacy of arsenic trioxide in a mouse *sarcoma* model and indicates that arsenic trioxide was only efficacious when it was coadministered with an antidote.[10] The article states that DNA composition blockage occurred in the *sarcoma* cells transplanted into the mice, and does not state or suggest that DNA composition blockage occurs in cancerous cells other than sarcoma cells.[11] Although the Office asserts that "Shimotsuura et al...confirm the DNA composition blockage action of arsenic trioxide antineoplastic,"[12] as just discussed, the Shimotsuura article indicates that DNA composition blockage occurred only in sarcoma cells, and does not teach or suggest that DNA compositions blockage occurs in other types of cancerous cells.

Finally, the Smith patent describes a device that can be used to deliver radiation to tissues that line body cavities, such as the bladder and colon, and states that the device can be used to treat tumors in such cavities.

The cited references thus indicate that arsenic preparations have been demonstrated to be efficacious in humans against skin cancer, cervical cancer, and leukemia, and in mice against sarcoma. The references do not provide data indicating that arsenic preparations have been demonstrated to be efficacious against any other tumor types. As discussed in the reply filed September 15, 2006, those skilled in the art would have appreciated at the time of the invention that the efficacy of a particular anti-cancer agent against a specific type of cancer, such as cervical cancer, was not predictive of its efficacy against other types of cancers, such as colon, ovarian, renal, bladder, and prostate cancers. It was understood that "[i]ncreasingly disease-specific therapies are being developed that will have optimum application for only one tumor type, although representing ineffective and toxic treatment for others."[13] Indeed, the therapeutic agents most commonly used to treat cancers at the time of the invention (and

[10] Table 4.
[11] Page 20 of the English translation.
[12] Office action dated December 1, 2006, page 4.
[13] *Medical Oncology*, Calabresi, P., *et al.*, eds., 1985, Macmillan Publishing Company, page 257 (copy enclosed as Exhibit A in the response filed September 15, 2006).

at present, as well) were effective only against specific types of cancers, and generally did not exhibit broad efficacy against numerous cancer types.[14] Accordingly, those skilled in the art at the time of the invention would not have reasonably expected that a combination of arsenic trioxide and radiation could have been successfully used to treat colon, ovarian, renal, bladder, or prostate cancer in humans just because arsenic had been reported to have efficacy in humans against skin cancer, cervical cancer, and leukemia and against sarcoma in mice. Although those skilled in the art might arguably have considered trying to use a combination of arsenic trioxide and radiation to treat cancers in humans other than skin and cervical cancers and leukemia, the results of doing so could not have been predicted with a reasonable degree of certainty. Accordingly, based upon the teachings of the 391 patent, those skilled in the art at the time of the invention would not have reasonably expected that a combination of arsenic trioxide and radiation could have been successfully used to treat colon, ovarian, renal, bladder, or prostate cancer in humans. The Office has not offered any convincing evidence to the contrary, and has thus failed to meet its burden of establishing *prima facie* obviousness.

The Office has unfortunately misinterpreted some of the statements made by applicants in the reply to the official action dated June 23, 2006 that was filed September 15, 2006. For example, the Office states that "Applicant notes that the CN 1079391 patent states 'they are still unable to touch upon in vivo cancer tumors,' but the quoted part there relates to a prior art survey, not the invention of CN 1079391."[15] In contrast to the Office's assertion, in making the statement quoted by the Office, applicants were actually referring to the prior art arsenic preparations described in the 391 patent:

> The 391 patent indicates that the use of arsenic preparations had been reported in the literature for the treatment of skin and cervical cancers. The patent then generalizes these findings by stating that arsenic preparations have been used for the treatment of "body surface and cavity cancers," ***but further states that the arsenic preparations described in the literature*** have a "range of application [that] is quite narrow, and they are still unable to touch upon in vivo cancer tumors....Some of the dosage forms are not advantageous to industrialized mass production, some are not convenient to use, and for some it is difficult to control the quality between batches during production." The patent indicates that the invention therefore involves the development of new

[14] *Id.* at 295-297.
[15] Office action dated December 1, 2006, page 6.

> arsenic-containing formulations and dosage forms to be used for the treatment of body surface and body cavity tumors.[16]

In addition, the Office states that applicant "erroneously asserts" that the Zhang patent limits its teaching regarding the described arsenic composition's effect on cell membranes, and on DNA/RNA synthesis, to leukemic cells.[17] Applicants actually directly quoted the following passage from the patent, however:

> Laboratory experiments indicate that the composition shows a strong abruptive effect on the membranes of leukemic cells. It also inhibits DNA/RNA synthesis in such cells, reduces the rate of proliferation of leukemic cells and destroys the leukemic cells.[18]

This portion of the patent is, in fact, limited to a discussion of the arsenic composition's effect on leukemic cells, as applicants noted in their reply.[19] As discussed above, another portion of the patent states that "[e]xperimental results demonstrate that the intravenous composition of the present invention exert [*sic*] a strong abruptive effect on the membranes of cancer cells, such as leukemic cells."[20] The patent, however, provides no experimental evidence, and does not cite or refer to anything in the literature that provides experimental evidence, demonstrating that arsenic compositions have an abruptive effect on the membranes of any type of cancer cells other than leukemic cells.

Since the office has failed to meet its burden of establishing that those skilled in the art would have reasonably expected that a combination of arsenic trioxide and radiation could have been successfully used to treat colon, ovarian, renal, bladder, or prostate cancer in humans at the time of the invention, the Office has failed to establish *prima facie* obviousness. Applicants accordingly, respectfully request withdrawal of the rejection.

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[16] Reply to the official action dated June 23, 2006 filed September 15, 2006, page 5.
[17] Official action dated December 1, 2006, page 7.
[18] Col. 2, lns. 23 to 27.
[19] Reply to the official action dated June 23, 2006 filed September 15, 2006, page 6.
[20] Col. 1, lines 58 to 61.

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Conclusion

Applicants believe that the foregoing constitutes a complete and full response to the official action of record. Accordingly, an early and favorable action is respectfully requested.

Respectfully submitted,

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